## REMARKS

Applicants request reexamination and reconsideration of the subject application pursuant to and consistent with 37 C.F.R. § 1.112 in light of the following:

## STATUS OF CLAIMS

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination.

It is respectfully pointed out that, while the other claims under examination have been rejected, Claims 12 and 66 are not indicated to be rejected in the Office Action Summary or in the rejection set forth in page 4 of the Office Action. Clarification is requested.

## INFORMATION DISCLOSURE STATEMENTS

Applicants thank the Examiner for considering the documents cited in their Fifth Information Disclosure Statement filed July 6, 2009. A Sixth Information Disclosure Statement is filed herewith. The document listed on the accompanying form PTO-1449 is discussed in the remarks which follow.

## REJECTION WITHDRAWN

The Examiner's previous rejection under 35 U.S.C. § 103(a) based on Schultz et al. in view of Baert et al. has been withdrawn.

## CLAIM REJECTIONS - 35 U.S.C. § 103

Amended Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. US Patent No. 6,194,395, in view of Wrenn Jr. US Patent No. 6,174,873 and in view of Loftsson et al. US Patent 6,699,849. Applicants believe that this rejection is untenable against any of the claims in this application.

## APPLICANTS' INVENTION

While the Examiner has withdrawn his previous obviousness rejection based on Schultz et al. in view of Baert et al., the Examiner nevertheless clings to his interpretation of particular features of Schultz et al. to the exclusion of what the Schultz et al. patent as a whole teaches to one of ordinary skill in the art.

First, applicants would like to once again draw the Examiner's attention to the essential features of applicants' invention as set forth in independent Claims 56 and 1, as well as in Claim 82.

Claim 56 is drawn to a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of: (a) an amorphous inclusion complex of cladribine with the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin (HPβCD) and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, said complex cladribine-cyclodextrin complex having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. This is a complex complex of cladribine and hydroxypropyl-β-cyclodextrin (HPβCD) in which there is an intimate mixture consisting of two different complexes, first an amorphous inclusion complex of cladribine and HPβCD (itself an amorphous cyclodextrin) and secondly a non-inclusion complex in which amorphous free cladribine is associated with the amorphous cyclodextrin HPβCD, and moreover this complex complex has a very particular weight ratio of cladribine to HPβCD of from about 1:10 to about 1:16.

The cladribine/ HPβCD complex of the invention has many properties that distinguish it from a mere mixture of hydroxypropyl-β-cyclodextrin and cladribine as was fully and convincingly shown by the data provided in the Van Axel Castelli et al. document provided with applicants' previous response and discussed in great detail therein.

The unique cladribine/hydroxypropyl-β-cyclodextrin complex defined in Claim 56 is an essential feature of applicants' unique pharmaceutical composition as claimed in Claim 1. Claim 1 is drawn to a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with the amorphous

cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. Thus, in addition to the special features of the complex complex itself as already discussed, it is essential that the pharmaceutical composition comprise no significant amount of free crystalline cladribine therein and that the complex complex be formulated into a solid oral dosage form. Neither the complex complex nor the pharmaceutical composition comprises any significant amount of free crystalline cladribine; this is excluded from the complex complex by use of the closed "consisting of" language in defining the components of the admixture therein.

Claim 82 is a product-by-process claim which specifies the steps applicants have found to provide the unique pharmaceutical composition of Claim 1, which in turn contains as an essential feature the precisely defined unique complex complex of Claim 56. Thus, Claim 82 is drawn to a pharmaceutical composition according to Claim 1 obtainable by a process comprising the steps of:

(i) combining cladribine and the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin in water at a temperature of from about 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

The time and temperature conditions set forth in part (i) are especially critical to formation of the Claim 56 complex complex and ultimately to formation of the Claim 1 pharmaceutical composition.

The Examiner relies upon Schultz et al. for disclosing a solid pharmaceutical dosage form comprising cladribine and cyclodextrin at column 2, lines 31-39. These lines do not indicate the nature of the relationship between the cladribine and the cyclodextrin. However, as applicants pointed out to the Examiner previously, Schultz et al. elsewhere disclose that their oral solid dosage forms contain a mixture of cladribine and cyclodextrin; see column 1, lines 8-10. Reference to solid mixtures is

also made by Schultz et al. in column 5, lines 50-64. Schultz et al. teach inclusion complex formation in solution but only to form injectable solutions. As to ratios, Schultz et al.'s weight ratios for their solid oral dosage form are 1 mg to 15 mg of cladribine and 100 mg to 500 mg of cyclodextrin (col. 6, lines 23-31). This does not lead one of ordinary skill to "instantly envision" a cladribine:cyclodextrin ratio ranging from 15 mg:100mg to 15 mg:500 mg, but rather from 1 mg:500 mg to 15 mg:100 mg. This is not 1:6.67 to 1:33.3, it is 1:500::1:6.67, a much broader ratio range than that stated by the Examiner. Further, as applicants previously pointed out, Schultz et al.'s ratio is for a mixture, not for a complex. Virtually any ratio could be present in a mixture. Such does not suggest what ratios would be not only possible but also advantageous in a complex.

While applicants agree that Schultz et al. do not disclose any of the many features noted by the Examiner in the paragraph spanning pages 5-6 of the Official Action, it is pointed out that Schultz et al. also do not suggest applicants' complex complex (as defined in Claim 56) or a pharmaceutical composition comprising applicants' complex complex formulated into a solid oral dosage form comprising no significant amount of free crystalline cladribine (as defined in Claim 1) or a process for preparing such a pharmaceutical formulation (as defined in Claim 82). However, what is missing from Schultz et al. is not supplied by the secondary references, Wrenn, Jr. and Loftsson et al.

It is agreed that the Wrenn, Jr. patent is directed to solid formulations for oral administration and that the adenosine analogs therein include cladribine. Wrenn, Jr.'s teaching in column 12, lines 25-30 is part of his discussion of an INDAS system. As noted at line 25, INDAS takes the form of a high energy matrix tablet. Production of that matrix tablet involves including adenosine analogs in an amorphous form together with a combination of energy, excipients and unique processing procedures. Wrenn, Jr. goes on to state (col. 12, lines 30-40) that once included in the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel polymer cross-linked technology to prevent recrystallization. The combination of the change in the physical state of the adenosine analogs coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the adenosine analogs. The resulting absorbed

amorphous drug complex granulate may then, according to Wrenn, Jr., be formulated with a gel-forming erodable tablet system to promote substantially smooth or continuous absorption. As set forth in Wrenn, Jr.'s Claim 1, his oral dosage form comprises an acid-labile 2'-deoxyadenosine analog which chemically decomposes in the acid environment and one or more components which inhibit that decomposition selected from the group consisting of erodible matrix, enteric coating, solid dispersion and ion exchange resin. In Claim 8, Wrenn, Jr. specifies that the composition is in a controlled-release mechanism. In Claim 10, the controlled-release mechanism may be an INDAS system, among others. Thus, while Wrenn, Jr. suggests amorphous forms of the drug, this is in the context of its being only one part of the INDAS system he is describing. Wrenn, et al. in no way suggests cyclodextrin complexation, much less how to make or how to use the specific complex complex of applicants' claims, which has nothing to do with novel polymer cross-linking technology. Indeed, cyclodextrins are not polymers and do not provide cross-linking! Wrenn, Jr. neither discloses nor suggests what applicants have done, which is to provide an intimate admixture consisting of (a) an amorphous inclusion complex of cladribine with HPβCD, and (b) amorphous free cladribine associated with said HPβCD as a non-inclusion complex, which is formulated into a solid oral dosage form comprising no significant amount of free crystalline cladribine therein, the cladribine:HPβCD ratio being from about 1:10 to about 1:16. There is no cladribine/cyclodextrin inclusion complex in Wrenn, Jr. and there is no non-inclusion complex there either, much less the remotest suggestion of applicants' invention as claimed herein. Indeed, Wrenn, Jr. is not remotely relevant to the present invention.

We turn now to Loftsson et al., which does indeed relate to cyclodextrins. Indeed, the very Loftsson and Brewster cyclodextrin review article referenced on page 18 of applicants' July 6, 2009 response and previously made of record in applicants' Third Information Disclosure Statement is referenced in column 2, lines 20-24 of the Loftsson et al. patent relied upon by the Examiner. Applicants already acknowledged many basic teachings in the cyclodextrin art, including the amorphous nature of HPβCD. Applicants agree that the statements made by the Examiner on page 6 of the Official Action about cyclodextrins are correct, with one notable exception. Loftsson et al do not teach that purine derivatives are, without

qualification, compatible with cyclodextrin for forming complexes. The Examiner has taken page 9, lines 50-55 completely out of context, as explained below.

The Loftsson et al. patent is aimed at enhancing the cyclodextrin complexation efficiency of certain structural classes of drugs by relying on reversible ring opening. In the OBJECTS AND SUMMARY OF THE INVENTION in columns 4-6, the Examiner's attention is drawn in particular to column 5, line 43 to column 6, line 49, where various aspects of the Loftsson et al. invention are summarized. In each of these aspects, the drug is defined as "having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal..." (Emphasis added). See also the wording of the claims of Loftsson et al.'s PCT counterpart, WO 99/42111, submitted with the accompanying IDS, which repeat this language. (The US claims recite only benzodiazepines, all of which have a cycle imine structure.) Thus, when Loftsson et al. disclose in columns 8-9 groups of preferred drugs, the patentees are speaking in the context of the quoted language; in other words, their purines are not any purines but are only ones which are susceptible to reversible ring opening. In the case of purines, Loftsson et al. disclose that the drugs are preferably caffeine, theophylline, etophylline, proxyphylline or theobromine. It is immediately apparent that cladribine, whose structure is depicted on page 1 of the instant application and in column 1 of Schultz et al., does not have the requisite imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal structure and thus is not susceptible to reversible ring opening and it not appropriate for use in Loftsson et al.'s invention. Moreover, as would be readily apparent to one of ordinary skill, cladribine is a nucleoside analog; it is a purine base in glycosidic linkage with a sugar, which is a ribofuranose. Loftsson et al. do not remotely suggest nucleosides or nucleoside analogs.

Secondly, the process described by Loftsson et al. for complexing their drugs with cyclodextrin is conducted at a pH level below about 5, preferably between about 3 and about 5, in the case of basic drugs such as benzodiazepine. See column 10 and the Examples, especially beginning with Example 3. The work described is

carried out in solution. Generally, the suspension of drug in aqueous cyclodextrin solution is heated in a sealed container in an autoclave, presumably to encourage ring openings at acidic pH. There is no specific disclosure of a solid oral dosage form that applicants can locate Furthermore, it is well-known that cladribine is acid-labile; as noted by Schultz et al., use of the compound orally has been limited by this fact. See col. 1, lines 36-51 of Schultz et al. Thus, one of ordinary skill would not be motivated to subject cladribine to the methods of Loftsson et al.'s patent, first because it does not even meet the structural requirements for use therein and secondly because it would decompose at the low pH levels favored by Loftsson et al. There is indeed no suggestion of cladribine in the Loftsson et al. patent.

While various methods of preparing drug-cyclodextrin complexes have been known in the art, applicants have found that a very carefully controlled series of steps are required to produce the instantly claimed complex complex and pharmaceutical composition containing it. The time and temperature specified in Claim 82 in step (i) are essential, for example, for production of applicants' unique products. The sum total of the conditions used by applicants together with the fact that cladribine is a nucleoside analog and thus has not only a particular purine ring but also a ribofuranose sugar ring surprisingly gives a very complex product when combined with HPβCD, because the hydroxyl groups on the ribofuranose ring in cladribine are able to hydrogen-bond to the hydroxyls on the exterior of the cyclodextrin ring, while the purine ring of cladribine is able to be at least partially included in the cavity of the cyclodextrin ring. This provides a very unique result which could not have been predicted. The present invention takes advantage of both parts (purine base + sugar) of the structure of cladribine so as to provide an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with HPβCD and (b) amorphous free cladribine associated with HPβCD as a non-inclusion complex (which is multiple hydrogen bond mediated as explained above), which then is further formulated into a solid oral dosage form, the composition comprising no significant amount of free crystalline cladribine therein, the composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. There is no suggestion in the art of this complex complex or of how to obtain it; the cited references in combination fail to lead one of

ordinary skill to this result. Thus, the subject matter of Claims 1, 5 and 82 is free of the outstanding rejection. The same is true of independent Claims 13 and 25 which contain all of the limitations of Claim 1. The more specific claims herein are even more remote from the prior art.

With respect to the product-by-process claims, applicants agree that the product of Claim 82 is the same as the product of Claim 1. Claims 82-90 and 94-98 are, however, patentable for all of the reasons set forth above with respect to Claim 1.

## CONCLUSION

In view of the foregoing, it is submitted that all claims in this application are free of the record rejections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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